Idiopathic Interstitial Pneumonias

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Abstract: The idiopathic interstitial pneumonias (IIPs) are a group of diffuse parenchymal lung diseases of unknown etiology characterized by the presence of various degrees of inflammation and fibrosis. Confident definitive diagnosis of the various IIPs requires dynamic interaction among clinicians, radiologists, and pathologists to arrive at a clinico-radiologic-pathologic diagnosis. The aims of this manuscript are to summarize the characteristic clinical and histologic manifestations, and to describe and illustrate the high-resolution computed tomography manifestations of the IIPs. The focus will be on idiopathic pulmonary fibrosis (idiopathic usual interstitial pneumonia), nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, and acute interstitial pneumonia. High-resolution computed tomography plays an important role in the initial diagnosis, the assessment of disease extent, the likelihood of response to treatment and prognosis, and the assessment of complications.

Key Words: idiopathic interstitial pneumonias, usual interstitial pneumonia, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, acute interstitial pneumonia

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Idiopathic interstitial pneumonias (IIPs) are a group of diffuse parenchymal lung diseases of unknown etiology with varying degrees of inflammation and fibrosis.[1] Several classifications for IIPs have been proposed. The most widely accepted scheme is the 2002 American Thoracic Society/European Respiratory Society (ATS/ERS) consensus classification.[1] This classification divides the IIPs into 7 clinicopathologic entities: idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (AIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), and lymphoid interstitial pneumonia. However, it is well recognized that RB-ILD and DIP are seldom idiopathic, the vast majority of cases representing a reaction to cigarette smoke.[2,3] These 2 conditions are therefore better classified as smoking-related interstitial lung diseases (see pages 274–284 review of smoking-related lung diseases by Dr Jeffrey Galvin). Although lymphoid interstitial pneumonia may rarely manifest as an IIP, it presents most frequently as a benign lymphoproliferative disorder that occurs almost exclusively in patients with underlying immunologic disorders, most commonly Sjögren syndrome[4] (see pages 299–309 review of lung disease related to collagen vascular disease by Dr David Lynch). The focus of this review will therefore be limited to IPF, which is synonymous with idiopathic usual interstitial pneumonia (UIP), idiopathic NSIP, COP, and AIP. As emphasized by the ATS/ERS classification, the final diagnosis of these entities requires dynamic interaction among clinicians, radiologists, and pathologists to arrive at a clinico-radiologic-pathologic diagnosis, the gold standard no longer being the histology but rather a multidisciplinary approach.[1,5]

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IDIOPATHIC PULMONARY FIBROSIS

IPF is defined as a distinctive type of chronic fibrosing interstitial pneumonia of unknown cause limited to the lungs and associated with the histopathologic pattern of UIP.[1] UIP is, as the name implies, the most common of the IIPs, accounting for 50% to 60% of cases.[5] UIP is a histologic diagnosis and a lung reaction pattern to injury. It may occur secondary to exposure to dusts (eg, asbestos) or drugs (eg, bleomycin), or may be observed in hypersensitivity pneumonitis (HP) or in association with collagen-vascular diseases (eg, rheumatoid arthritis).[1] When, after careful clinical evaluation, no etiology is found, it is classified as an IIP, and in this context it is considered synonymous with IPF.[1] IPF has a poor prognosis, with a median survival of 2.5 to 3.5 years after the time of diagnosis.[1,6]

Patients with IPF typically present with a 6-month to 2-year history of progressive shortness of breath and a dry cough (Table 1).[1] The vast majority of patients are over 50 years of age and the mean age at presentation is 66 years.[6] IPF is more common in smokers and ex-smokers than in lifelong nonsmokers, and more common in men than in women, the male:female ratio being approximately 1.5:1.[6,7] On physical examination, finger clubbing is observed in 25 to 50% of cases, and on auscultation late inspiratory crackles (Velcro rales) are characteristic.[1] Pulmonary function tests show a restrictive pattern with reduced lung volumes and impairment in gas exchange.[8,9]

UIP is characterized histologically by a patchy heterogeneous pattern with foci of normal lung, interstitial inflammation, fibrosis, and honeycombing (Table 1).[1,10] The histologic abnormalities therefore reflect different stages in the evolution of fibrosis, a combination of old and active lesions; this is termed ''temporal heterogeneity'' and is characteristic of UIP.[1,10] Another characteristic histologic feature is the presence of fibroblastic foci, that is, aggregates of proliferating fibroblasts and myofibroblasts that represent microscopic zones of acute lung injury set against a backdrop of chronic fibrosis.[10] The fibrosis and honeycombing typically involve mainly the basal and subpleural lung regions.[10,11] Lack of subpleural honeycombing on surgical lung biopsy should suggest an alternative diagnosis.[12]

TABLE 1. Clinical, Histologic, and HRCT Features of Idiopathic Interstitial Pneumonias

	Idiopathic Pulmonary Fibrosis	Nonspecific Interstitial Pneumonia	Cryptogenic Organizing Pneumonia	Acute Interstitial Pneumonia
Clinical findings				
Mean age, range (y)	66 (40-80)	52 (9-78)	58 (15-87)	59 (7-83)
Male:Female ratio	1.5:1	1:3	1:1	1:1
Typical duration of symptoms	6 mo to 2 y	3 to 24 mo	3 wk to 6 mo	d to wk
5 y Mortality	70%	10%	< 5%	60%
Histologic findings				
Temporal appearance	Heterogeneous	Uniform	Uniform	Uniform
Interstitial inflammation	Scant	Prominent	Mild	Scant
Organizing pneumonia	No	Occasional, but limited	Yes	No
Fibroblastic foci	Prominent	Occasional	No	Diffuse
Fibrosis	Yes, patchy	Variable, diffuse	Absent or mild	No until late stage
Honeycombing	Yes	Uncommon	No	In late stage
HRCT findings				
Reticulation	Usually predominates	Common; mild-to-moderate	Uncommon; mild if present	Common in late stage
Ground-glass opacity	Mild or absent	Commonly predominates	Common	Common
Consolidation	Uncommon	Common; usually mild	Typically predominates	Common mainly dependent lung
Honeycombing	Usually present	Uncommon	No	In late stage
Predominant distribution	Peripheral and basal	Basal	Peribronchial, peripheral, perilobular	Diffuse

High-resolution Computed Tomography Findings

The characteristic high-resolution computed tomography (HRCT) manifestations of IPF are reticulation and honeycombing, which are usually bilateral and symmetric, and in 70% to 95% of patients involve mainly the subpleural regions and lung bases (Table 1) (Fig. 1).[13–15] The distribution is most commonly bilateral and symmetric, although it can sometimes be asymmetric. The reticular pattern results from a combination of intralobular lines and irregular septal thickening, but the lobular architecture is often so distorted that these may be impossible to recognize.[12,16,17] Dilated and distorted bronchioles (ie, traction bronchiolectasis) and bronchi (traction bronchiectasis) are frequently visible within the areas of reticulation (Fig. 2).[1,16,18] Honeycomb cysts have been reported on HRCT at presentation in 24% to 91% of patients with IPF.[15,16,19] Honeycomb cysts usually range from 2 to 20 mm in diameter.[17,20] They typically seem to share walls on HRCT and usually manifest as a single row or several layers of cysts in the subpleural lung (Fig. 1).

Ground-glass opacity is commonly visible on HRCT in patients who have IPF, but is typically less extensive than the reticular pattern (Fig. 2).[13,21] It may indicate the presence of potentially reversible disease,[22] presence of fibrosis below the resolution of HRCT,[23] or areas of honeycombing filled with secretions.[24] Ground-glass opacity should be considered to represent an active process only when there are no associated HRCT findings of fibrosis. Findings of fibrosis in association with ground-glass opacity include intralobular interstitial thickening, honeycombing, and traction bronchiectasis and bronchiolectasis.[23]

Other findings described in patients with IPF include areas of decreased attenuation and vascularity in 4% to 43%, small areas of consolidation in 3%, and a few centrilobular nodules in 2% to 15%.[15,21,25] Occasionally, fine linear or small nodular foci of calcification are observed within areas of fibrosis as a result of ossification (Fig. 3).[26] Kim et al[27] found disseminated dendriform pulmonary ossification on HRCT in 5 of 75 patients (6.7%) with IPF compared with none of 44 patients with NSIP. As IPF is more common in smokers and ex-smokers, HRCT may show emphysema involving mainly the upper lung zones (Fig. 4). The association between emphysema and IPF is typically accompanied by marked reduction in diffusing lung capacity for carbon monoxide and the presence of larger lung volumes than in never-smoking patients with IPF.[28,29]

Mild mediastinal lymph node enlargement is evident on CT in approximately 70% of patients with IPF.[30–32] The lymphadenopathy usually involves only 1 or 2 nodal stations, and the nodes usually measure less than 15 mm in short axis diameter (Fig. 5).[30,31] The likelihood of lymphadenopathy increases with the extent of parenchymal involvement and decreases in the presence of recent steroid treatment.[33]

Acute Exacerbation of Idiopathic Pulmonary Fibrosis

Follow-up studies have shown only minor changes in the HRCT in the first 6 months after diagnosis,[34] but progressive increase in the extent of reticulation and honeycombing 1 year or more after diagnosis.[35–37] This progression most commonly occurs gradually over several months or years (Fig. 6). However, some patients develop a fulminant and often fatal acute exacerbation.[38] The clinical diagnosis of acute exacerbation of IPF is based on rapid deterioration (30 d or less), new bilateral radiographic opacities (typically ground-glass and consolidation), and absence of demonstrable infection or other identifiable etiology.[39] The reported prevalence of acute exacerbation ranges from 9.6% (11 of 147 patients with IPF) over 2 years[40] to 57% (32 of 56) of patients over 3 years,[41] and the mortality from 53% to 78%.[40,41] In one prospective study of 168 patients with

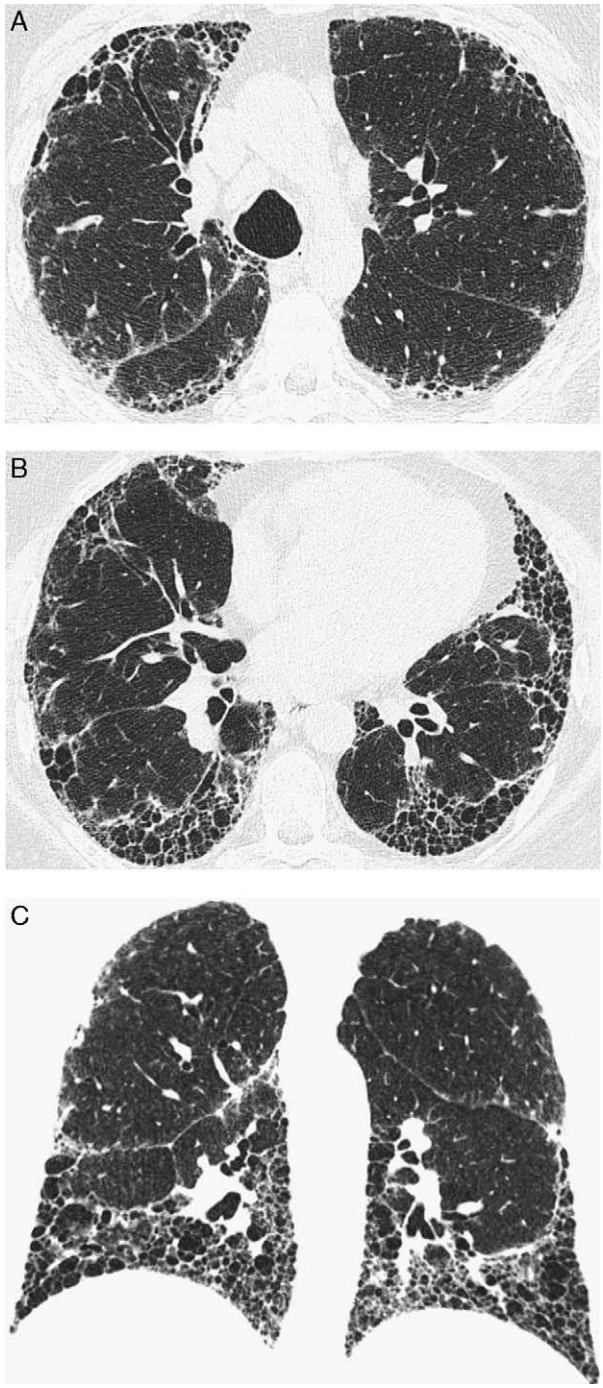

FIGURE 1. Typical HRCT findings of idiopathic pulmonary fibrosis in a 59-year-old man. A, HRCT image at the level of the upper lobes shows bilateral peripheral reticulation and honeycombing. B, HRCT image at the level of lung bases shows greater extension of peripheral honeycombing. C, Coronal reformation image shows mild peripheral reticulation in the upper lobes and extensive reticulation and honeycombing in the lower lung zones.

mild-to-moderate IPF, 36 (21%) died after a follow-up of 76 weeks; 15 of the deaths were acute, including acute exacerbation of IPF in 6 (40%), pneumonia in 4, acute respiratory distress syndrome (ARDS) in 2, cor pulmonale in 1, and unknown cause in 2.[42]

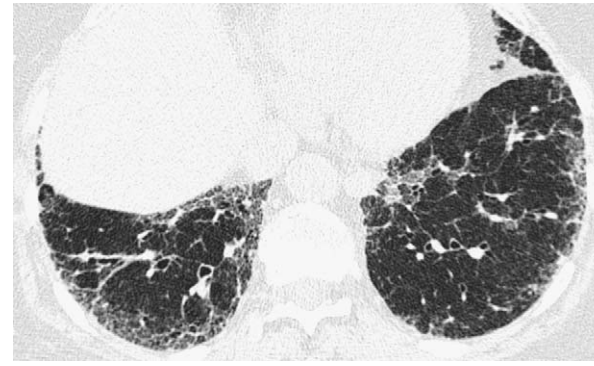

FIGURE 2. A case of idiopathic pulmonary fibrosis without honeycombing on HRCT in an 83-year-old man. HRCT image at the level of the lung bases shows extensive peripheral reticulation with associated dilatation and distortion of the bronchioles (traction bronchiolectasis). Although there are some foci of ground-glass opacity, these are limited to areas with reticulation, and therefore probably represent microscopic fibrosis. Note the absence of definite honeycombing.

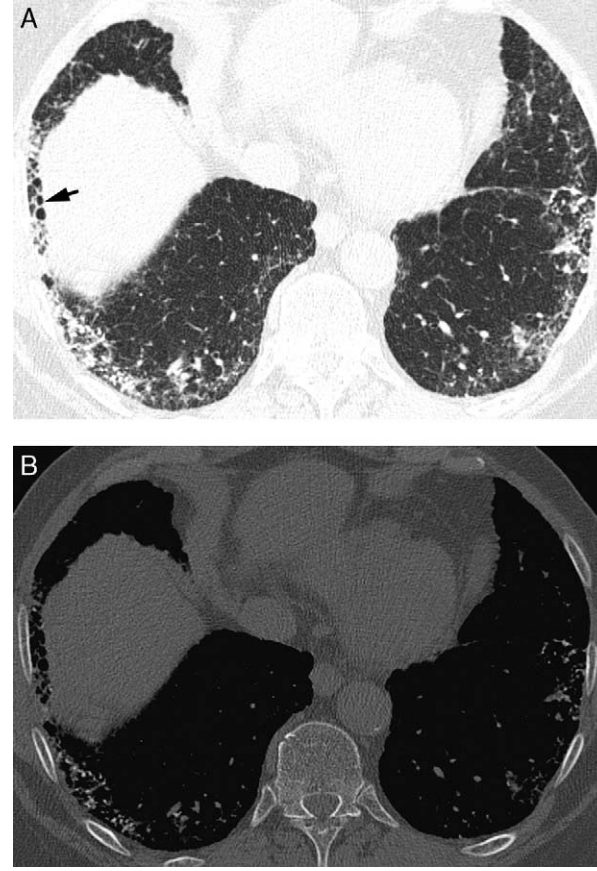

FIGURE 3. Pulmonary ossification in idiopathic pulmonary fibrosis in an 80-year-old man. A, HRCT image at the level of the right hemidiaphragm photographed at lung windows shows peripheral reticulation, mild honeycombing (arrow), and several small nodular opacities. B, HRCT image photographed at soft tissue windows shows calcified small nodules within the areas of reticulation consistent with pulmonary ossification.

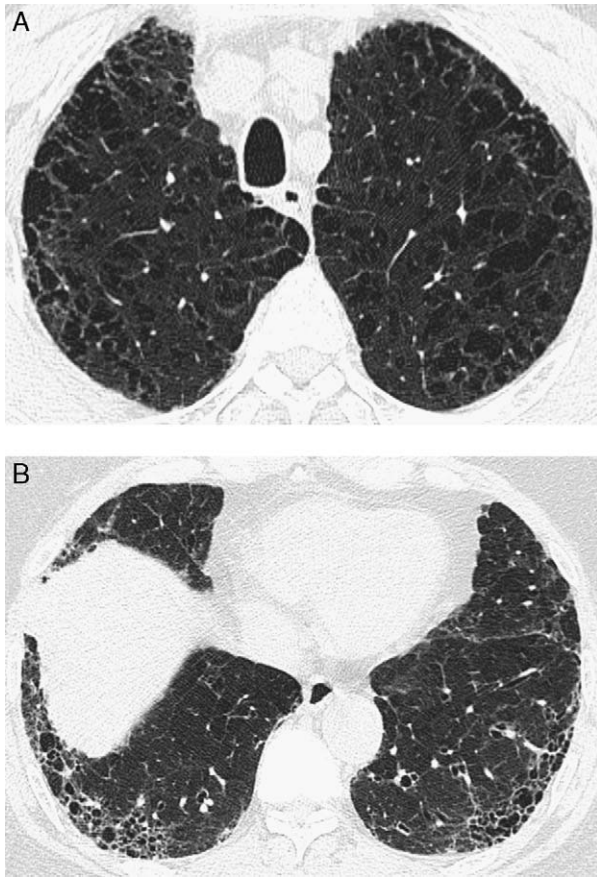

FIGURE 4. Emphysema and idiopathic pulmonary fibrosis in a 70-year-old man. A, HRCT image at the level of the upper lobes shows extensive centrilobular emphysema. B, HRCT image at the level of the dome of the right hemidiaphragm shows mild emphysema and peripheral reticulation and honeycombing.

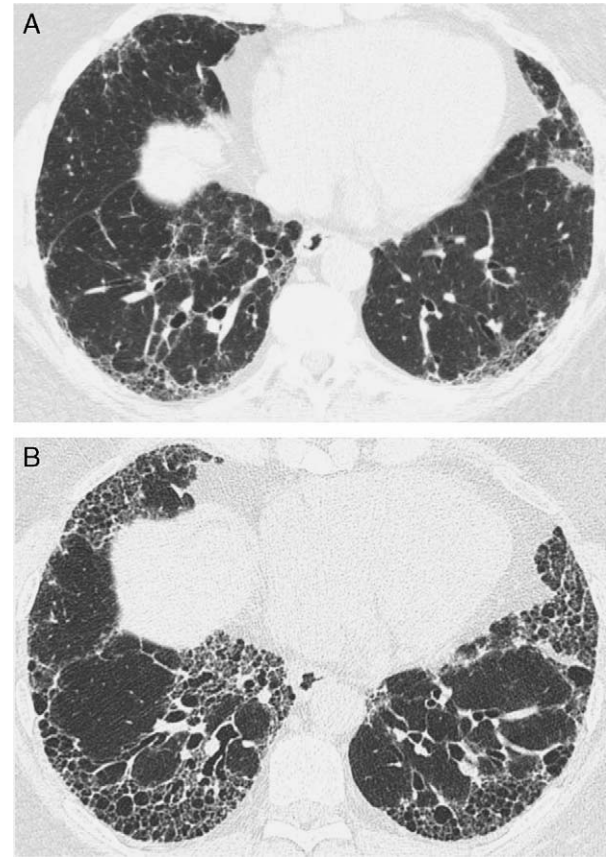

FIGURE 6. Progression of usual interstitial pneumonia on follow-up. A, HRCT image at the level of the lower lung zones shows mild peripheral reticulation with associated traction bronchiolectasis and ground-glass opacities. B, HRCT image performed 3 years later shows marked increase in the extent of reticulation and development of subpleural honeycombing.

The histologic findings of acute exacerbation of IPF consist of diffuse alveolar damage (DAD) or extensive organizing pneumonia superimposed on the UIP pattern.[43,44] The HRCT manifestations consist of ground-glass opacities and/or consolidation superimposed on reticulation and honeycombing (Fig. 7).[44–46] The ground-glass opacities and consolidation may be diffuse, multifocal, or peripheral.[44,46] The consolidation tends to involve mainly the dorsal half of the lung. Patients with peripheral ground-glass opacities have a better prognosis than patients with multifocal or diffuse opacities.[44–46] However, the histologic findings are a better predictor of prognosis than the CT findings. Patients with acute exacerbation of IPF who have organizing pneumonia are more likely to respond to treatment than patients with DAD.[45] The main differential diagnosis of acute exacerbation on HRCT in patients with known IPF and acute clinical deterioration is opportunistic infection, particularly *Pneumocystis jiroveci* pneumonia.

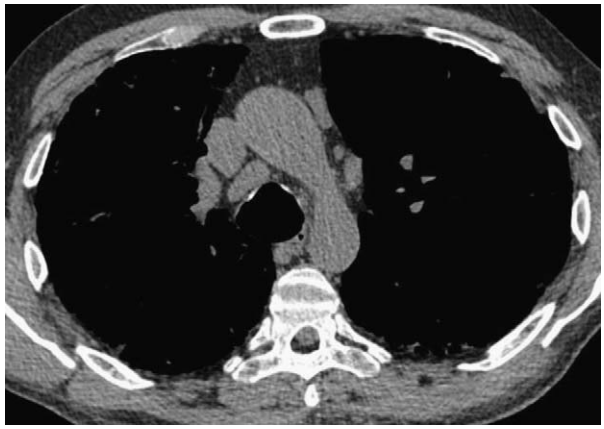

FIGURE 5. Lymph node enlargement in idiopathic pulmonary fibrosis in a 59-year-old man. Computed tomography image shows slightly enlarged paratracheal lymph node and normal size prevascular nodes.

NONSPECIFIC INTERSTITIAL PNEUMONIA

NSIP is a chronic interstitial lung disease characterized by relatively homogeneous expansion of the alveolar walls by inflammation and/or fibrosis.[10,47,48] NSIP accounts for 14% to 35% of biopsies performed for chronic interstitial pneumonia.[10] NSIP may be idiopathic, but more commonly occurs as a manifestation of collagen vascular disease, HP, drug-induced lung disease, or chronic interstitial lung

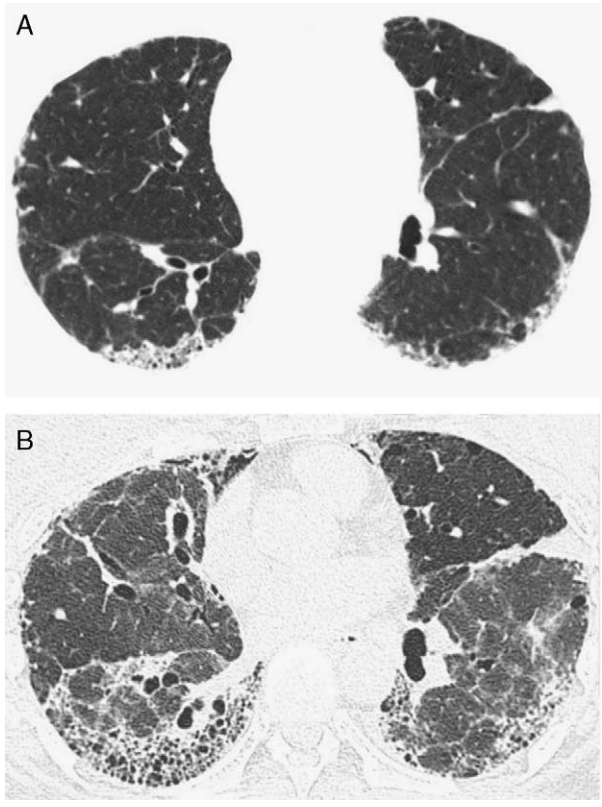

FIGURE 7. Acute exacerbation of idiopathic pulmonary fibrosis in a 53-year-old woman. A, HRCT image at the level of the lower lung zones shows mild peripheral reticulation and traction bronchiolectasis. B, HRCT image 1-year later when the patient presented with acute-onset shortness of breath and hypoxia shows progression of fibrosis with increase in the reticulation and development of honeycombing. Also noted are extensive bilateral ground-glass opacities and pneumomediastinum. Surgical biopsy showed diffuse alveolar damage superimposed on a background of usual interstitial pneumonia.

disease complicating DAD.[10,47] These conditions must be excluded before making a diagnosis of idiopathic NSIP. Distinction of idiopathic NSIP from IPF is important because NSIP has a considerably better prognosis, the 5-year survival being approximately 80%[48,49] compared with approximately 30% for IPF.[49–51]

The histologic hallmark of NSIP is its relative temporal and geographic homogeneity, the findings seeming to represent the same stage in the evolution of the disease, as distinct from the heterogeneity observed in UIP (Table 1).[10,48] The histologic findings may range from a predominantly inflammatory process (ie, cellular NSIP) to predominant fibrosis (ie, fibrotic NSIP). In cellular NSIP, the alveolar septa are thickened by infiltrates of lymphocytes and plasma cells, whereas in fibrotic NSIP the thickening is a result of collagen accumulation.[10] The fibrosis in NSIP is typically of the same age with preservation of the alveolar architecture.[48] Honeycombing is uncommon, not being observed histologically in any of the 67 patients with NSIP recently reviewed by a panel of expert pathologists.[48] The presence of fibrosis in NSIP is associated with a worse prognosis.[1] Patients with an exclusively inflammatory component (ie, cellular NSIP) have an excellent prognosis with few reported deaths, whereas the reported median survival of patients with fibrotic NSIP ranges from approximately 6 to14 years.[5] The prognosis of NSIP, whether cellular or fibrotic, is therefore considerably better than the prognosis of IPF.[1]

The average age of presentation is approximately 52 years (Table 1),[48] but ranges from 9 to 78 years of age.[1,48] Approximately 2/3 of patients are female and 70% are lifelong nonsmokers.[48] Clinically, patients present with symptoms similar to IPF, dyspnea and cough, but the duration is more variable, ranging from 1 month to 10 years (median 7 mo).[1]

HRCT Findings

The most common HRCT manifestations of NSIP are ground-glass opacities, irregular linear (reticular) opacities, traction bronchiectasis, and lower-lobe volume loss (Table 1) (Fig. 8).[13,48,52,53] Although most studies have shown predominant ground-glass opacities,[13,52,53] a recent study of 67 patients reviewed by a panel of expert chest radiologists showed a reticular pattern in 87%, traction bronchiectasis in 82%, lower-lobe volume loss in 77%, and ground-glass attenuation in only 44% of patients.[48] Honeycombing has been described on HRCT in 5% to 30% of patients, and when present tends to be mild, involving less than 10% of the parenchyma.[13,48,52–54] Areas of consolidation have been reported in several studies,[25,48,52,53] but were not observed in one other large study.[13] It should be emphasized that it is uncommon for consolidation to be the main abnormality in NSIP. When chronic consolidation is present in a patient with NSIP, it most commonly reflects a component of associated organizing pneumonia, and is often associated with underlying fibrosis and traction bronchiectasis.[55] At histology, organizing pneumonia may be observed in up to two-thirds of cases,[1] but usually involves less than 10% to 20% of the overall biopsy specimen.[48]

The parenchymal abnormalities in NSIP involve mainly the lower lobes in approximately 90% of patients (Fig. 8) and all lung zones to an equal extent in the remaining 10% of patients.[48] The abnormalities are commonly diffuse in the transverse plane, but in approximately 35% of patients involve mainly the peripheral regions and in 20% to 65% of patients show relative sparing of the immediate subpleural lung in the dorsal regions of the lower lobes (Fig. 8).[25,48,54]

Patients with NSIP and only ground-glass opacities on HRCT typically have cellular (inflammatory) NSIP. However, patients with ground-glass opacities, reticulation, and traction bronchiectasis may have cellular or fibrotic NSIP.[21,56] Johkoh et al[52] compared the HRCT findings of the subtypes of NSIP in 55 patients. There was no appreciable difference in the extent of ground-glass opacities (average extent 30% of the parenchyma), consolidation (average extent 10%), small nodules (average extent 9%), or interlobular septal thickening (average extent 5%) between cellular and fibrotic NSIP. Thirteen of 33 (39%) patients with fibrotic NSIP had honeycombing. Patients with fibrotic NSIP also had a greater extent of intralobular lines (reticulation) (12% vs. 8%) and traction bronchiectasis (15% vs. 5%) than patients with cellular NSIP.[52] Tsubamoto et al[56] compared the HRCT findings in 6 patients with predominantly interstitial inflammation, 15 with an equivalent extent of inflammation and fibrosis,

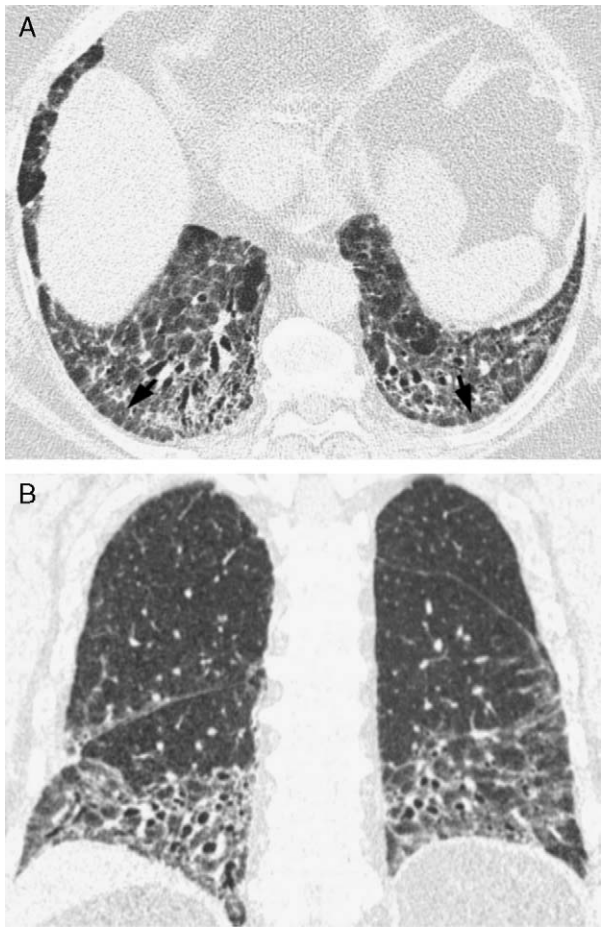

FIGURE 8. Nonspecific interstitial pneumonia in a 71-year-old woman. A, HRCT image at the level of the lung bases shows extensive bilateral ground-glass opacities, reticulation, and traction bronchiectasis. Note relative sparing of the lung (arrowheads) immediately adjacent to the pleura in the dorsal lung regions of the lower lobes (relative subpleural sparing). Although there is ground-glass opacity in the subpleural lung, the reticulation and traction bronchiectasis are approximately 1 cm away from the pleura. B, Coronal reformation image shows ground-glass opacities, reticulation, and traction bronchiectasis mainly in the lower lung zones.

and 15 with predominantly fibrosis on lung biopsy. The extent of ground-glass opacities in the 3 groups was similar, with an average extent ranging from 25% to 35% of the lung parenchyma. All 3 groups had an average extent of consolidation of 10%. The extent of intralobular linear opacities (reticular pattern) ranged from an average of 13% of the parenchyma in patients with predominant inflammation to an average of 23% in patients with predominant fibrosis. The extent of traction bronchiectasis ranged from an average of 18% in patients with predominant inflammation to 23% in patients with predominant fibrosis. Honeycombing was not observed in any patient with predominant inflammation or equivalent inflammation and fibrosis, but was observed in patients with predominant fibrosis (average extent 4%).[56]

It is important to note that the pattern of abnormalities of NSIP may change over time, and closely resemble UIP. Silva et al[54] retrospectively assessed the change in disease pattern of NSIP (n = 23) and UIP (n = 25) over a follow-up period of 34 to 155 months. Follow-up CT in patients with NSIP showed marked decrease in the extent of ground-glass opacity, increase in reticulation, and a greater likelihood of peripheral distribution (all $P < 0.05$). At presentation, the CT findings were interpreted as suggestive of NSIP in 18 of 23 patients with NSIP and indeterminate or suggestive of IPF in 5. In 5 (28%) of 18 patients with initial findings suggestive of NSIP, the follow-up CT scans were interpreted as more suggestive of IPF.[54] No CT features observed at presentation allowed distinction between patients with NSIP that maintained an NSIP pattern at follow-up and those that progressed to an IPF pattern.

Mediastinal lymph node enlargement is evident on CT in approximately 80% of patients.[30,31] The nodal enlargement is usually mild, with lymph nodes measuring 10 to 15 mm in short-axis diameter and involving only 1 or 2 nodal stations (most commonly the right lower paratracheal or subcarinal region). The likelihood of lymphadenopathy increases with greater extent of disease.[30,31] The prevalence of mediastinal lymphadenopathy in NSIP is similar to that in IPF.[30,31]

Acute Exacerbation of Nonspecific Interstitial Pneumonia

Similar to patients with IPF, patients with NSIP may develop acute deterioration with an abrupt worsening of symptoms owing to infection, pulmonary embolism, pneumothorax, or heart failure. Occasionally, however, no identifiable cause for the acute decline is identified, and these episodes are called "acute exacerbation" or the "accelerated phase" of NSIP.[43,45] Acute exacerbation of NSIP is considerably less common than acute exacerbation of IPF, having been described in a small number of patients.[43,45] The histologic findings consist of DAD or organizing pneumonia superimposed on a background of NSIP.[43] The HRCT findings consist of extensive ground-glass opacities and/or consolidation superimposed on reticulation.[45]

CRYPTOGENIC ORGANIZING PNEUMONIA

Organizing pneumonia is a histologic pattern characterized by the presence of intraluminal plugs of granulation tissue within alveolar ducts and surrounding alveoli associated with chronic inflammation of the surrounding lung parenchyma.[1] Granulation tissue polyps may be also present in the respiratory bronchioles. Therefore, the condition is also known as bronchiolitis obliterans organizing pneumonia (BOOP).[57] Organizing pneumonia is a common reaction pattern observed in association with pulmonary infection, connective tissue diseases, inflammatory bowel disease, inhalational injury, HP, drug toxicity, radiation therapy, and aspiration.[1,58,59] In some patients, however, no underlying cause is found, and the condition is termed "COP"[60] or idiopathic BOOP.[57] Because the clinical, functional, radiologic, and HRCT findings are primarily the result of an organizing pneumonia, the ATS/ERS Multidisciplinary Consensus Classification Committee recommended that the condition be named COP rather than idiopathic BOOP.[1]

Patients who have COP typically present with a 2-to-3 month history of nonproductive cough.[1,61] Other common manifestations include low-grade fever, malaise, and shortness

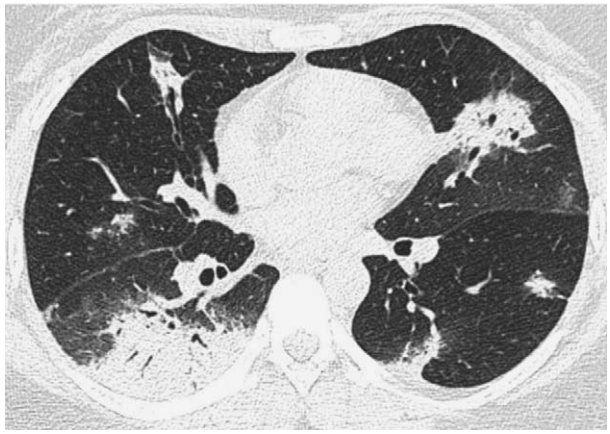

FIGURE 9. Cryptogenic organizing pneumonia in a 56-year-old man. HRCT image at the level of the inferior pulmonary veins shows patchy bilateral consolidation in a peribronchial and peripheral distribution, and mild ground-glass opacities.

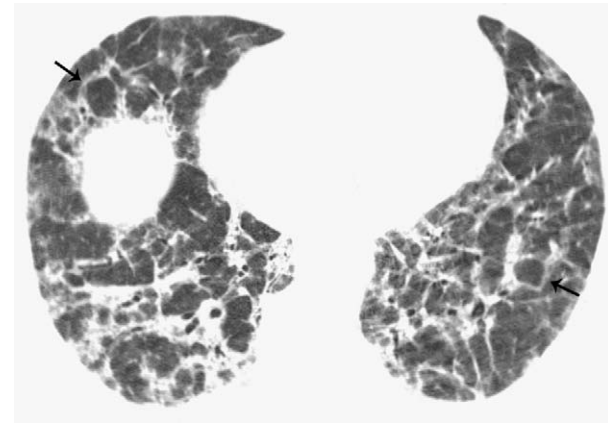

FIGURE 10. Cryptogenic organizing pneumonia in a 59-year-old man. HRCT image at the level of the dome of the right hemidiaphragm shows perilobular opacities (arrows). Also noted are foci of peribronchial consolidation, mild reticulation, and extensive bilateral ground-glass opacities.

of breath.[1,60–62] COP is equally common in men and women, but nonsmokers outnumber smokers by 2:3.[1,61] The mean age at presentation is 58 years (range 15 to 87).[63] The patients usually respond well to corticosteroid therapy and have a good prognosis.[1,61]

HRCT Findings

The characteristic HRCT manifestations of COP consist of patchy unilateral or, more commonly, bilateral consolidation (observed in 80% to 90% of cases), which in 60% to 80% of cases has a subpleural and/or peribronchial distribution (Fig. 9) and a perilobular pattern (observed in 60% of cases) (Table 1).[64–67] The perilobular pattern is defined as poorly defined band-like opacities that are of greater thickness than those encountered in thickened interlobular septa and that have an arcade-like or polygonal appearance (Fig. 10).[67] Bronchial wall-thickening and dilatation may be observed on HRCT in patients who have extensive consolidation, and is usually restricted to these areas.[64,68] Ground-glass opacities are observed in approximately 60% of patients, usually in association with areas of consolidation.[66] Occasionally, ground-glass opacities may be the predominant or only manifestation of COP on HRCT.[66] The ground-glass opacities are usually bilateral and random in distribution. Crazy-paving pattern, that is, a superimposition of ground-glass opacity and interlobular septal thickening, may also be observed.[69] COP often involves the lower lung zones to a greater degree than the upper lung zones.

Less common findings include small, ill-defined peribronchial or centrilobular nodules[64,70]; large nodular or mass-like areas of consolidation[71]; areas of ground-glass opacity surrounded by a ring-like or crescentic opacities (reversed halo or atoll sign) (approximately 20% of patients);[72,73] and irregular linear opacities (reticulation) (7% to 29%).[64,66,73] Irregular linear opacities (reticulation) in patients with COP are usually associated with consolidation and located in the subpleural or peribronchial regions of the lower lung zones. Occasionally, the reticular opacities may be the predominant HRCT finding.[68]

Extrapulmonary findings in patients who have COP include small pleural effusions, present in 10% to 30% of patients,[64,66,73] and mild right paratracheal or subcarinal lymphadenopathy, observed in 20% to 40% of cases.[30,73] The pleural effusions are small and may be unilateral or bilateral.[66]

ACUTE INTERSTITIAL PNEUMONIA

AIP is a fulminant disease of unknown etiology that usually occurs in a previously healthy person and is characterized by histologic findings of DAD (Table 1).[1,74] Because the clinical presentation and the histologic features are identical to those of ARDS, AIP has also been referred to as idiopathic ARDS.[75] The average age at presentation is approximately 59 years (range 7 to 83 y).[1,76] It has no sex predominance and no association with cigarette smoking. There is often a prodromal illness associated with symptoms of a viral upper respiratory infection followed

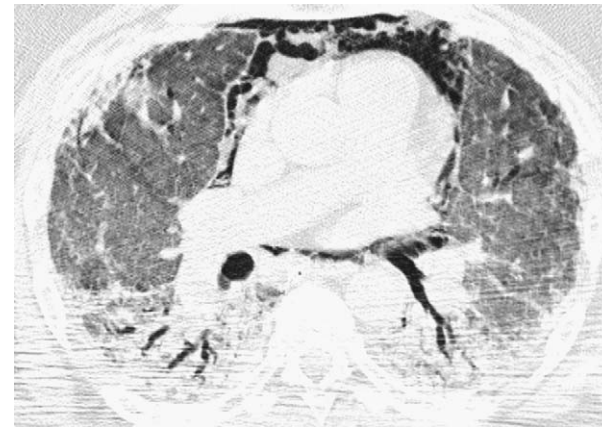

FIGURE 11. Acute interstitial pneumonia in a 65-year-old man. HRCT image at the level of the bronchus intermedius shows diffuse bilateral ground-glass opacities and areas of consolidation mainly in the dependent lung regions. Also noted is pneumomediastinum. Surgical biopsy showed diffuse alveolar damage.

by dry cough and rapidly progressive severe dyspnea and respiratory failure. The majority of patients have symptoms for less than 1 week before diagnosis.[77] The prognosis is poor, the mortality being 50% or more and most deaths occurring between 1 and 2 months of presentation.[74,75,77]

The histologic findings of AIP are those of DAD.[1,74,75] The acute, exudative phase shows edema, hyaline membranes, and acute interstitial inflammation. In the subacute, proliferative (organizing) phase there is prominent interstitial and airspace fibroblast proliferation and type 2 pneumocyte hyperplasia. In the chronic, fibrotic phase, typically 2 weeks or more after the injury, there is progressive fibrosis with collagen deposition.

HRCT Findings

The HRCT findings in the early stages of AIP (exudative phase) consist primarily of bilateral ground-glass opacities and areas of consolidation (Fig. 11) (Table 1).[18,78–80] The ground-glass opacities may be patchy or diffuse; focal sparing of lung lobules is frequently present, resulting in a geographic distribution.[81] Smooth septal thickening and intralobular lines are often observed superimposed on the ground-glass opacities ("crazy-paving" pattern).[79] The ground-glass opacities usually involve all lung zones, but may have lower or, less commonly, upper lobe predominance.[79] The airspace consolidation may be patchy or confluent, and tends to involve mainly the dependent lung regions (Fig. 11).[79]

The proliferative (organizing) phase and the fibrotic stages of AIP are characterized by the presence of architectural distortion and traction bronchiectasis. In a study by Akira,[78] these findings were observed only on CT scans obtained more than 7 days after the onset of symptoms. Honeycombing, present in a small percentage of patients with AIP, correlates with the presence of dense interstitial fibrosis and restructuring of distal airspaces.[80,81]

CLINICAL UTILITY OF HRCT

Diagnosis of Idiopathic Interstitial Pneumonias

The main role and clinical utility of HRCT is in the diagnosis of IPF and the distinction of IPF from other IIPs. It is currently widely accepted that a confident diagnosis of IPF can often be made on the basis of a combination of clinical and HRCT findings.[5,18,50] The high specificity of HRCT in the diagnosis of UIP and IPF was initially shown in several retrospective studies[82–84] and subsequently confirmed in 2 prospective studies, both of which only included patients with biopsy-proven diagnosis and used histologic features as gold standard.[85,86] The first prospective study was by Raghu et al,[85] who assessed the accuracy of a clinical diagnosis of IPF and interstitial lung diseases other than IPF in 59 patients who were referred for evaluation of new-onset interstitial lung disease. A specific clinical diagnosis was independently made by a clinician who was an expert in interstitial lung diseases after a thorough clinical assessment that included evaluation of the HRCT findings. The chest radiographs and CT scans were separately reviewed by the thoracic radiologist, who made a radiologic diagnosis independently. The sensitivity and specificity of the IPF diagnosis by the clinical expert were 62% and 97%, respectively. The sensitivity and specificity of the radiologic first-choice diagnosis of IPF were 78% and 90%, respectively.[85] Hunninghake et al[86] performed a prospective multicenter investigation of 91 patients, including 54 patients with biopsy-proven IPF. The sensitivity of HRCT for a confident diagnosis of IPF by experienced chest radiologists was 48% and the specificity and positive predictive values were 95% and 96%, respectively.[86] On the basis of these studies, it is now well accepted that in the appropriate clinical setting the presence of characteristic HRCT findings allows confident noninvasive diagnosis of IPF, obviating lung biopsy.[1,87] It should be noted, however, that diagnostic HRCT findings of UIP/IPF are only present in 50% to 70% of patients (Fig. 2). When the HRCT findings do not allow a confident diagnosis or when the clinical findings are atypical (eg, potential exposure to an antigen, raising the possibility of HP), surgical lung biopsy is indicated.

A confident HRCT diagnosis of IPF requires clinical exclusion of known causes of UIP and the presence of all the following 3 HRCT criteria: presence of a reticular pattern in a predominantly peripheral and basal distribution, presence of honeycombing in a predominantly peripheral and basal distribution, and absence of atypical features (eg, centrilobular nodules, peribronchovascular nodules, extensive consolidation, or extensive ground-glass opacities).[15,86] If only the first and third criteria are present, namely, if honeycombing is absent, the findings can only be interpreted as "probable IPF".[15] The strongest predictors of IPF on HRCT are lower-lung honeycombing (odds ratio, 5.36) and upper-lung reticulation (odds ratio, 6.28).[14] Although basal and peripheral honeycombing is a strong predictor of IPF, there is surprisingly considerable interobserver disagreement in the diagnosis of honeycombing.[15] Confident diagnosis of honeycombing requires the presence of clustered cystic airspaces measuring 2 mm to 1 cm in diameter that have well-defined thick walls and are located adjacent to the pleura. They must be distinguished from traction bronchiolectasis, which may have a similar appearance but typically is located a few mm or more from the pleura.

It should be noted that surgical lung biopsy also has limitations. Most importantly, it is invasive and usually assesses only a small part of the lung. Thus, the region sampled may not be representative of the lung as a whole, and the presence of inflammation may be missed. Furthermore, different lobes may show different pathology. For example, in one review of the surgical lung biopsy specimens obtained from 2 or more lobes in 109 patients with a clinical syndrome of IPF and a histologic pattern of either UIP or NSIP, 51 patients had a histologic UIP pattern in all lobes (concordant UIP), 33 patients had NSIP in all lobes sampled, and 28 (26%) had both NSIP and UIP (ie, discordant UIP).[88] In another review of the multiple surgical lung biopsy specimens obtained in 64 patients with suspected IPF, 39% had concordant UIP, 48% had concordant NSIP, and 13% had both UIP and NSIP (discordant UIP).[49] Only by correlating the CT with the pathologic findings can an overall evaluation of the pattern and extent of lung disease be adequately assessed.

Although a confident diagnosis of IPF can often be made on the basis of the clinical and HRCT findings, there is considerable overlap between the HRCT findings in NSIP and those present in other interstitial lung diseases, particularly IPF and HP, precluding confident diagnosis of NSIP on HRCT.[53,89] For example, Johkoh et al[89] reviewed the HRCT findings in 129 patients who had various IIPs,

including 27 patients who had NSIP. Two independent observers made a correct first-choice diagnosis, on average, in 71% of cases of UIP, 79% of cases of COP, and 63% of cases of DIP, but in only 9% of cases of NSIP. In none of the cases of NSIP was the diagnosis made with a high degree of confidence on HRCT. More recent studies, however, have shown a higher accuracy of HRCT in distinguishing between NSIP and UIP. For example, MacDonald et al[13] compared the HRCT findings of UIP and NSIP in 53 consecutive patients who had a clinical presentation consistent with IPF and who underwent lung biopsy. The final diagnosis was IPF in 32 patients and NSIP in 21. HRCT had a sensitivity of 63% and a specificity of 70% for UIP and a sensitivity of 70% and a specificity of 63% for NSIP. The most helpful finding in distinguishing NSIP from UIP was the greater extent of ground-glass opacities (odds ratio: 1.04 for each 1% increase in the proportion of ground-glass opacities).[13] Elliot et al[90] reviewed the HRCT scans of 47 patients with biopsy-proven IPF (n = 22) and NSIP (n = 25). A confident CT diagnosis of IPF and NSIP was correct in 88% and 73% of cases, respectively. The presence of honeycombing as a predominant feature had a specificity of 96%, sensitivity of 41%, and a positive predictive value of 90% for IPF. This pattern was identified in only a single patient (by both readers) with fibrotic NSIP. Conversely, predominant ground-glass opacity and/or reticular opacity with minimal or no honeycombing was identified in 48 (96%) of 50 readings in patients with NSIP, and in 26 (59%) of 44 readings in patients with UIP, giving a sensitivity of 96% and a specificity of 41% for the diagnosis of NSIP.[90] Sumikawa et al[21] compared the HRCT findings of various IIPs in 92 patients with biopsy-proven diagnosis. Two independent observers made the correct diagnosis in 79% of readings. Multivariate logistic regression analysis showed that the most useful finding for distinguishing IPF from NSIP was the extent of honeycombing. The average extent of honeycombing was 4.4% of the parenchyma in IPF, 0.3% in cellular NSIP and 0.6% in fibrotic NSIP.[21] Another helpful finding in distinguishing NSIP from IPF is the relative subpleural sparing in the dorsal regions of the lower lobes observed at 2 or more levels in up to 65% of patients with NSIP compared with only 4% of patients with UIP[25] (Fig. 12). In summary, these studies show that in many patients HRCT allows distinction of NSIP from IPF. However, while the presence of predominantly peripheral and basal honeycombing in the appropriate clinical setting often allows a confident diagnosis of IPF on HRCT, a confident diagnosis of NSIP requires surgical biopsy.

Although a definitive diagnosis of NSIP usually requires surgical biopsy, in clinical practice surgical biopsy is underused and performed in fewer than 15% of patients with chronic interstitial lung disease.[91,92] Even if patients undergo lung biopsy, there is considerable disagreement among pathologists over the diagnosis of interstitial lung diseases, particularly NSIP.[93] Furthermore, a histologic diagnosis of NSIP often does not constitute a final diagnosis, because NSIP is a common reaction pattern to various drugs; is commonly associated with collagen vascular diseases, particularly scleroderma; and can be a histologic manifestation of HP.[1,10] These conditions need to be excluded by careful clinical assessment before making a diagnosis of idiopathic NSIP. Moreover, in many cases even expert clinicians, pathologists, and radiologists fail to reach a consensus as to the diagnosis. Churg and Müller[94] therefore proposed an alternative approach to the IIPs and morphologically and radiologically related conditions such as HP, interstitial lung disease in collagen vascular disease, and drug-related interstitial lung disease. Their approach is based on dividing the radiologic or histologic findings into 3 types: (a) purely cellular processes, with or without a component of organizing pneumonia; (b) processes that show the type of linear fibrosis (fibrosis that follows the original alveolar walls) without architectural distortion as observed in fibrotic NSIP, some cases of chronic HP, and some drug reactions, with or without a cellular component; and (c) processes that show the fibrotic architectural distortion of UIP, namely, honeycombing.[94] Processes that

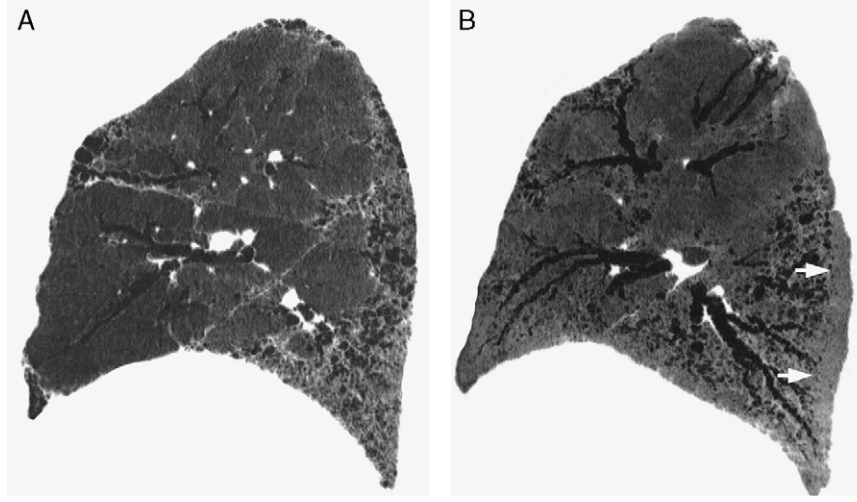

FIGURE 12. Usual interstitial pneumonia and nonspecific interstitial pneumonia: comparison of distribution in dorsal subpleural lung regions. A, Sagittal reformation minimal intensity projection HRCT image in a patient with usual interstitial pneumonia shows diffuse involvement of the dorsal lung regions. B, Sagittal reformation minimal intensity projection HRCT image in a patient with nonspecific interstitial pneumonia shows extensive reticulation and traction bronchiectasis in the lower lung zones, but sparing the immediately subpleural lung in the dorsal regions of the lower lobes (arrows).

are purely cellular, including RB-ILD, DIP, cellular NSIP, COP, and subacute (nonfibrotic) HP, usually respond to corticosteroid therapy. Thus, regardless of the specific diagnosis or label of the disease, if the process is purely cellular it usually responds to treatment. Linear fibrosis without architectural distortion is associated with a distinctly worse prognosis than purely cellular lesions. This has been well documented for patients with NSIP,[95] and patients with chronic HP and fibrosis.[96] This classification is particularly practical and helpful for cases in which the clinical, histologic, and radiologic features do not fit neatly into the ATS/ERS classification of IIPs, nor with a diagnosis of HP.[94]

The diagnosis of HP can often be strongly suggested by a combination of history of exposure to a known offending antigen; recurrent episodes of symptoms; symptoms occurring 4 to 8 hours after exposure; and characteristic HRCT findings of bilateral ground-glass opacities, lobular areas of decreased attenuation with air-trapping on expiratory images, and poorly defined centrilobular nodules.[97,98] However, in up to 40% of histologically proven cases of HP, the offending antigen is not identified.[96,97] Furthermore, in patients with chronic HP the HRCT findings may mimic those of IPF and NSIP.[98,99] Silva et al[25] compared the HRCT findings of 18 patients with proven chronic HP, 23 with IPF, and 25 with NSIP. Two independent chest radiologists assessed the HRCT images, made a first-choice diagnosis, and noted the degree of confidence in the diagnosis. The CT features that best differentiated chronic HP were lobular areas with decreased attenuation and vascularity, poorly defined centrilobular nodules, and absence of lower-zone predominance of abnormalities ($P \leq 0.008$). The features that best differentiated NSIP were relative subpleural sparing, absence of lobular areas with decreased attenuation, and lack of honeycombing ($P \leq 0.002$). The features that best differentiated IPF were basal predominance of honeycombing, absence of relative subpleural sparing, and absence of centrilobular nodules ($P \leq 0.004$). A confident diagnosis was made in 70 (53%) of 132 readings by the 2 observers. This diagnosis was correct in 66 (94%) of 70 readings. The authors concluded that the characteristic CT features of chronic HP, IPF, and NSIP allow confident distinction among these entities on HRCT in approximately 50% of patients.

The HRCT findings of COP are relatively nonspecific, and may be observed in a variety of infections and neoplastic diseases.[18,71] However, COP can usually be readily distinguished from other chronic interstitial and airspace lung diseases on HRCT. Johkoh et al[89] reviewed the HRCT findings in 129 patients who had various IIPs, including 24 with COP. On average, on the basis of the pattern and distribution of abnormalities on HRCT, 2 independent observers made a correct first-choice diagnosis in 79% of 24 cases of COP.[89] In patients with clinical and CT findings consistent with COP, the diagnosis can usually be readily confirmed by transbronchial biopsy showing characteristic histologic features of organizing pneumonia and exclusion of other causes of organizing pneumonia by clinical history and laboratory tests.

The predominant subpleural distribution of COP resembles that of chronic eosinophilic pneumonia (CEP). Arakawa et al[100] compared the HRCT findings in 38 patients with COP and 43 patients with CEP. Air-space consolidation was the most frequent HRCT finding in both COP (87%) and CEP (74%), and it had a predominately peripheral distribution in 66% of patients with COP and 56% of patients with CEP. A peribronchial distribution of consolidation was observed more frequently in COP than in CEP (29% vs. 9%). There was no appreciable difference in the cephalocaudal distribution of the consolidation between COP and CEP. The most helpful distinguishing feature on CT was the presence of nodules, observed in 32% of patients with COP and only 5% of patients with CEP. On the basis of the HRCT findings, 2 independent chest radiologists made a correct first choice of COP or CEP in 67% and 72% of cases, respectively.[100] In clinical practice, the differential diagnosis can be readily made on the basis of clinical history and laboratory tests. Approximately 50% of patients with CEP have asthma and the vast majority has peripheral eosinophilia.[101]

The HRCT findings of AIP reflect the presence of DAD, and are therefore similar to those of ARDS of known etiology. However, Tomiyama et al[102] showed that patients with AIP are more likely to have a symmetric lower-lobe distribution of abnormalities and a greater prevalence of honeycombing (26% of patients vs. 8%). In clinical practice, the vast majority of patients with DAD have a known etiology, the diagnosis of AIP requiring careful clinical evaluation to eliminate less common causes of DAD such as drug reaction or collagen vascular disease.

Prognosis of Idiopathic Interstitial Pneumonias

Both the long-term survival in IPF and its likelihood of response to treatment with corticosteroids correlate with the histologic and HRCT findings. In the past it was believed that alveolitis played an important role in the development of fibrosis and that the prognosis was influenced by the extent of inflammation histologically[103,104] and by the extent of ground-glass opacity on HRCT.[105,106] These studies preceded the description of NSIP in 1994,[47] and almost certainly included patients with IIPs other than IPF, particularly NSIP. Furthermore, the theory that inflammation eventually leads to widespread pulmonary fibrosis seems to hold true for several of the corticosteroid-responsive IIPs (eg, NSIP), but not for UIP.[91] More recent studies have shown that the extent of reticulation and honeycombing are better predictors of prognosis than the extent of ground-glass opacities. For example, a study by Gay et al[107] showed that although the extent of ground-glass opacities was higher in corticosteroid responders than in nonresponders, the only CT parameter that statistically predicted death during follow-up of patients with IPF was the extent of lung fibrosis. More recently, in a retrospective study of 167 patients with IPF, Best et al[108] showed that visually determined extent of fibrosis on HRCT is a strong independent predictor of mortality in IPF. Flaherty et al[109] showed that among patients with IPF, an HRCT showing characteristic features of IPF, namely, honeycombing, was associated with worse survival than an HRCT showing findings more suggestive of NSIP (no honeycombing) (median survival, 2.1 vs. 5.8 y) and worse than patients with a histologic diagnosis of NSIP (median survival > 9 y).[109] Jeong et al[110] found that patients who have IPF and minimal or no honeycombing (ie, honeycombing involving less than 5% of the parenchyma) on HRCT had a mortality rate similar to those with NSIP, and significantly lower than those with UIP and honeycombing. Overall, these studies show that

the prognosis of IPF is worse than that of NSIP, and that patients with IPF and honeycombing have worse prognosis than patients with minimal or no honeycombing.

Serial HRCT scans in patients with IPF typically show progressive increase in the extent and severity of fibrosis over several months or years.[35,111] Reticulation often progresses to honeycombing and honeycomb cysts increase in size (Fig. 6).[35,36] The areas of ground-glass opacities may improve or resolve with treatment or may progress to reticulation and honeycombing.[35,37] Serial CT scans in patients with NSIP have shown that patients with predominant ground-glass opacities on the initial CT are more likely to improve with treatment and have a better long-term prognosis than patients with predominant reticulation.[112–114] Screaton et al[114] performed serial CT scans in 38 patients with histologically proven NSIP, including 4 with cellular NSIP, 13 with mixed cellular and fibrotic NSIP, and 21 with fibrotic NSIP. The predominant initial CT pattern was inflammatory (ground-glass opacities and consolidation) in 6 (16%) patients and fibrotic (reticulation and honeycombing) in 32 (84%). At a mean follow-up of approximately 1 year, all of the patients with an inflammatory predominant pattern on the initial CT improved, whereas of the 32 patients with a fibrotic predominant pattern, 7 (22%) improved, 6 (19%) deteriorated, and 19 (59%) remained stable. Surprisingly, there was no significant association between the histologic findings and the likelihood of improvement on follow-up CT.[114]

The vast majority of patients with COP has predominant consolidation on HRCT and shows good response to corticosteroids. Predominant reticulation is observed in a small percentage of patients and is associated with worse prognosis. Lee et al[68] reviewed the HRCT findings of 26 patients with COP who had radiographic follow-up for a median of 44 weeks after treatment. Of the 26 patients, 17 (65%) had partial or complete resolution of the abnormalities at follow-up and 9 (35%) had persistent or progressive abnormalities. Consolidation was present on the initial CT scan in 14 (82%) of the 17 patients who improved on follow-up, but in only 2 of the 9 patients with persistent or progressive disease ($P = 0.009$). None of the 6 patients who had irregular linear opacities as the predominant pattern on initial HRCT showed complete resolution on follow-up imaging ($P = 0.02$).[68]

HRCT can also be helpful in predicting likelihood of response to treatment in patients with AIP. Ichikado et al[115] compared the HRCT findings of AIP between 10 survivors and 21 nonsurvivors. The extent of ground-glass opacity or air-space consolidation without traction bronchiectasis or bronchiolectasis was greater in survivors than in nonsurvivors, and the extent of either ground-glass opacity or air-space consolidation combined with traction bronchiolectasis or bronchiectasis was greater in nonsurvivors.

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